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Artesunate plus mefloquine versus mefloquine for treating uncomplicated malaria (Review)

Bukirwa H, Orton LC

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[Intervention Review]

Artesunate plus mefloquine versus mefloquine for treating uncomplicated malaria

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ABSTRACT

Background

Using a pilot system we have categorised this review as: “Historical question – no update intended: monotherapy no longer recommended" (see published notes).

Multiple-drug-resistant malaria is widespread, and in South-East Asia resistance is high against nearly all single therapy antimalarial drugs. Here, and in other areas with low malaria transmission, the combination of artesunate and mefloquine may provide an effective alternative.

Objectives

To compare artesunate plus mefloquine with mefloquine alone for treating uncomplicated *Plasmodium falciparum* malaria.

Search methods

We searched the Cochrane Infectious Diseases Group Specialized Register (May 2005), CENTRAL (*The Cochrane Library* Issue 2, 2005), MEDLINE (1966 to May 2005), EMBASE (1988 to May 2005), LILACS (May 2005), BIOSIS (1985 to June 2005), conference proceedings, and reference lists. We also contacted researchers, organizations, and pharmaceutical companies.

Selection criteria

Randomized and quasi-randomized controlled trials comparing artesunate plus mefloquine with mefloquine alone for treating uncomplicated malaria.

Data collection and analysis

Two authors independently applied the inclusion criteria, extracted data, and assessed methodological quality. The primary outcome was treatment failure by day 28, defined as evidence of parasitaemia with or without clinical failure between days zero (start of treatment) and 28. For dichotomous data we calculated risk ratios (RR) and 95% confidence intervals (CI).

Main results

Eight trials involving 1996 participants met the inclusion criteria. All were conducted in areas with low malaria transmission, seven in South-East Asia and one in the Peruvian Amazon. The doses and dosing regimens of artesunate and mefloquine varied across trials. The trials using a total dose of 25 mg/kg mefloquine and 10 mg artesunate reported fewer treatment failures with the combination at all time points: day 28 (RR 0.17, 95% CI 0.06 to 0.47; 824 participants, 4 trials), day 42 (RR 0.23, 95% CI 0.14 to 0.39; 298 participants, 1 trial), and day 63

(RR 0.26, 95% CI 0.09 to 0.77; 501 participants, 2 trials). The results for parasitaemia showed a similar trend. Trials using a lower dose of artesunate tended to favour the artesunate plus mefloquine combination. Overall, adverse events were similar across treatment arms.

Authors' conclusions

Artesunate plus mefloquine performs better than mefloquine alone for treating uncomplicated falciparum malaria in areas with low malaria transmission. A total dose of 25 mg/kg mefloquine and at least 10 mg artesunate leads to higher cure rates. Better reporting of methods and standardisation of outcomes would help the interpretation of future trials.

2008: As monotherapy is no longer recommended by the World Health Organization for malaria treatment, the authors do not intend to update this review.

23 April 2019

No update planned

Review superseded

Please refer to the Cochrane Special Collection: Sinclair 2014 https://doi.org/10.1002/14651858.SC000007/full

PLAIN LANGUAGE SUMMARY

Artesunate plus mefloquine in areas with low malaria transmission performed better than mefloquine alone for uncomplicated *P. falciparum* malaria

Using a pilot system we have categorised this review as: “Historical question – no update intended: monotherapy no longer recommended" (see published notes).

Malaria is a parasitic disease spread by mosquitoes that kills thousands of people worldwide. Multiple-drug-resistant malaria is widespread, and in South-East Asia resistance is high against nearly all single therapy antimalarial drugs. Here, and in other areas with low malaria transmission, the combination of artesunate and mefloquine may provide an effective alternative. The review includes eight trials, mainly from South-East Asia, that compared artesunate plus mefloquine with mefloquine alone for treating uncomplicated malaria. Artesunate plus mefloquine performed better at destroying blood parasites and reducing fever. Adverse events were similar with both treatments.

BACKGROUND

Plasmodium falciparum malaria continues to be a major cause of ill health and death in many areas, especially in the tropics (WHO/UNICEF 2003). Uncomplicated falciparum malaria is the commonest form of the disease and accounts for the greatest proportion of morbidity (Olliaro 1996).

Antimalarial combination therapy is currently regarded as a major strategy to combat drug-resistant malaria (RBM 2001a). This is because malaria parasites can rapidly develop resistance to antimalarial drugs when they are used alone (single therapy). Combination therapy involves the simultaneous use of two or more blood schizonticides (drugs acting on the blood stage of the malaria parasites) that have independent modes of action and different biochemical targets in the parasite (White 1999; RBM 2001b). The combination may be more effective than single therapy, if the components exert a synergistic or additive antimalarial effect and there is decreased effectiveness due to resistance to at least one of the component drugs. The combination of artemisinin derivatives with other antimalarial drugs is widely advocated because it produces rapid clinical and parasitological response, may delay the development of resistance, and may reduce malaria transmission (RBM 2001a).

Artesunate is a water-soluble derivative of dihydroartemisinin and the most widely used member of the artemisinin derivatives. It is effective against gametocytes (Price 1996), the sexual forms of the parasites responsible for the transmission of malaria, and is one of the most rapidly acting antimalarial agents available. There is no documented resistance against artesunate, but because it has a very short half life (less than two hours), long treatment courses of five to seven days are necessary to prevent recurrence of the parasites (Bethell 1997; White 1999).

Mefloquine is a 4-quinoline methanol antimalarial drug. It has been used as single therapy in areas of low malaria transmission and where chloroquine resistance is common (White 1996). Because its terminal half life is about 20 days, it is eliminated slowly from the body (Looareesuwan 1992b). This means that the malaria parasites are exposed to sub-therapeutic levels of the drug over long periods of time, which encourages the development of resistant strains (White 1997). Reports from Thailand and neighbouring countries show that parasites are rapidly developing resistance to mefloquine (Wongsrichanalai 2002), and its use as a single antimalarial treatment is no longer recommended in these areas (Looareesuwan 1998).

In South-East Asia, mefloquine is often combined with artesunate to treat multiple-drug-resistant uncomplicated malaria (Angus 2001). The rationale is to provide improved early clearance of parasites in order to reduce the probability of any remaining parasites surviving the residual effect of mefloquine. By preventing the exposure of the initial high load of parasites to mefloquine alone the spread of parasite resistance to mefloquine may be delayed. The gametocidal action of artesunate may also reduce the transmission of mefloquine-resistant malaria strains. The addition of mefloquine to artesunate allows the use of a practical short course of artesunate, that is, three days compared with five or seven days for artesunate alone. The combination may also reduce recrudescence rates; for example, recrudescence rates as high as 37% have been observed with a five-day course of artesunate compared with 7% when artesunate is given together with mefloquine (Price 1998; Trung 2001).

Results from clinical trials comparing artesunate plus mefloquine with mefloquine alone suggest that the combination is superior. These trials have however used varying regimens of the combination with mefloquine given either during or after the artesunate course (Hoshen 2000). In addition, current dosage schedules are based on available clinical data and not from well-designed dose-finding trials (RBM 2001c). Therefore, it is still unclear which regimen and dosing schedule are most suitable.

The use of artesunate and mefloquine either alone or in combination may be associated with unwanted effects. Mefloquine is associated with neuropsychiatric disorders, including psychosis and convulsions, which have been observed both during treatment and prophylaxis (Weinke 1991). Some artemisinin derivatives have been associated with fatal neurotoxicity in animals, and a few people taking artemisinin drugs have been reported with transient first-degree heart block, but artesunate itself seems to be well tolerated (Brewer 1994; Kain 1995; Gilles 2000). Reports from trials assessing the effects of the combination have reported moderate tolerability with no increase in adverse events over those related to the individual drugs (WHO 2002).

McIntosh and Olliaro prepared a Cochrane review of all artemisinin drugs for treating uncomplicated malaria (McIntosh 1999). Although they reviewed the effects of combining artemisinins with mefloquine, no two trials used the same treatment regimens and thus the findings were inconclusive. However, the review authors do not intend to update their review because their objectives were achieved. Our review attempts to answer the still outstanding questions regarding the combination of artesunate plus mefloquine.

OBJECTIVES

To compare artesunate plus mefloquine with mefloquine alone for treating uncomplicated *Plasmodium falciparum* malaria.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized and quasi-randomized controlled trials.

Types of participants

Adults and children with uncomplicated *P. falciparum* malaria, as confirmed by microscopy.

Types of interventions

Intervention

Artesunate plus mefloquine.

Control

Mefloquine.

Mefloquine dose should be the same in both the intervention and control groups.

Types of outcome measures

Primary

Treatment failure (parasitological) by day 28, defined as evidence of parasitaemia with or without clinical failure between day zero (start of treatment) and day 28.

Secondary

- Treatment failure (parasitological) by days 28, 42, and 63, excluding new infections where possible.
- Parasitaemia on thick blood film on days seven and 14.
- Resolution of fever: fever clearance time (time for temperature to return to normal as defined by the trial authors; and fever clearance within 48 hours of starting treatment).
- Parasite clearance: parasite clearance time; and rate of 50% and 90% parasite clearance (PC 50, PC 90) as reported.
- Number of participants developing severe malaria, as defined by the World Health Organization (WHO 2001), during follow up.
- Adherence (number of participants completing treatment).

Adverse events

- Number of adverse events.
- Serious adverse events: adverse events that lead to death, require hospitalization or prolongation of existing hospitalization, are life threatening, or result in persistent or significant disability or incapacity.
- Adverse events that require the discontinuation of treatment.
- Other adverse events.

Search methods for identification of studies

We attempted to identify all relevant trials regardless of language or publication status (published, unpublished, in press, and in progress).

Databases

We searched the following databases using the search terms and strategy described in Table 1: Cochrane Infectious Diseases Group Specialized Register (May 2005); Cochrane Central Register of Controlled Trials (CENTRAL) published in *The Cochrane Library* (Issue 2, 2005); MEDLINE (1966 to May 2005); EMBASE (1974 to May 2005); LILACS (1982 to May 2005); and BIOSIS (1985 to June 2005).

Conference proceedings

We searched the following conference proceedings for relevant abstracts: Third European Congress on Tropical Medicine and International Health, Lisbon, Portugal, 8 to 11 September 2002; and The Third Multilateral Initiative on Malaria Pan-African Conference, Arusha, Tanzania, 18 to 22 November 2002.

Researchers, organizations, and pharmaceutical companies

We circulated a list of the trials identified using this search strategy to organizations and individual researchers working in the field to help identify any additional trials. We also sought unpublished or confidential reports and information on ongoing trials. We contacted the following pharmaceutical companies: Arenco (France); Mepha (Switzerland); Rhone-Poulenc Rorer (France); Propharma (Scotland); Novartis (Switzerland); Sanofi-Winthrop (France); Guilin Pharmaceutical Company (China); Kunning Pharmaceutical Corporation (Malaysia); Thua Thien Pharmaceutical Company (Viet Nam); and the National Pharmaceutical Plant Company (Viet Nam).

Reference lists

We checked the reference lists of existing reviews (McIntosh 1999; McIntosh 2000) and of all trials identified by the above methods.

Data collection and analysis

Selection of studies

The first author scanned the results of the search strategy for all potentially relevant trials before retrieving the full articles and scrutinizing them for possible multiple publications. Both authors independently assessed each potentially relevant trial for inclusion in the review using an eligibility form based on the inclusion criteria. There were no disagreements. We give the reason for excluding trials in the 'Characteristics of excluded studies'.

Data extraction and management

Both authors independently extracted data using a data extraction form; there were no disagreements. The first author entered the data into Review Manager 5. For trials where some outcomes were not reported or were not clear, we wrote to the trial authors for more information.

We approximated intention-to-treat analysis wherever possible but generally the reports had insufficient information. We calculated the percentage loss to follow up and reported this information in the 'Characteristics of included studies'. For dichotomous outcomes, we recorded the number of participants experiencing the event in each group, and, for continuous outcomes, we extracted the arithmetic means and standard deviations.

Assessment of risk of bias in included studies

Both authors independently assessed the methodological quality of each included trial. We classed generation of allocation sequence and allocation concealment as adequate, inadequate, or unclear according to Jüni 2001. We described who was blinded, such as the participants, care provider, or outcome assessors, and classed the inclusion of all randomized participants in the final analysis as adequate if 90% or more were included.

Data synthesis

We analysed the data with Review Manager 5 using risk ratio (RR) for dichotomous data, mean difference(MD) for continuous data, and 95% confidence intervals (CI). Because the dose and regimen of both artesunate and mefloquine varied, we categorized trials based on total dose of artesunate and mefloquine used. We categorized artesunate as at least 10 mg/kg (multiple doses) and less than 10 mg/kg (single dose) and mefloquine as either 25 mg/kg or 15 mg/kg.

We assessed heterogeneity amongst trials by inspecting the forest plots and by using the chi-squared test for heterogeneity with a 10% level of statistical significance. We used the random-effects model where there was statistically significant heterogeneity and it was still appropriate to combine the trials.

Future updates

We were unable to use some methods in the protocol because there were too few trials, but we intend to use these methods, described in Table 2, in future updates.

RESULTS

Description of studies

See ' Characteristics of included studies ' for individual trial details.

Eight of 12 potentially relevant trials met our inclusion criteria. One trial was reported on in two separate publications (Marquino 2003), and two trials were reported in a single publication (Nosten 1994a; Nosten 1994b).

Source of funding

The trials were funded by various sources, including nongovernmental organizations (eg Médecins Sans Frontières), governmental organizations (eg US Agency for International Development and the Government of Peru), international organizations (eg World Health Organization), and pharmaceutical companies. The trial reports did not state the role of the funding agencies in the trial process.

Trial design and location

All trials were described as randomized, but most trial authors provided no information on the method of randomization. The trials were conducted in low malaria transmission areas. Seven trials were conducted in South-East Asia − Thai-Burmese border (two), Thai-Cambodia border (one), Thai-Myanmar border (one), most northern state of the Union of Myanmar (one), and the interior of Thailand (two). One trial was conducted in the Peruvian Amazon Basin in South America.

Participants

The eight trials included 1155 participants. Five trials included children and adults, and three trials included adults with the lowest cut-off age of 15 years.

Interventions

All trials compared artesunate plus mefloquine with mefloquine alone. Four trials had additional arms that were not considered in this review. As shown in Table 3, the total dose of artesunate and mefloquine varied across the trials; some trials used single doses and others divided the doses.

Drug resistance

The seven trials conducted in South-East Asia were in areas described as having multiple-drug-resistance to antimalarial drugs; nearly all mentioned high resistance to mefloquine. Marquino 2003 did not mention resistance to mefloquine, but it was likely to be low.

Outcome measures

All trials reported the presence of parasites at various time points in addition to other review outcomes. None reported on adherence to the treatment schedule or the progression to severe malaria. All trials except Smithius 2004 mentioned adverse events, although some did not report them in detail.

Risk of bias in included studies

See Table 4 *and the ' Characteristics of included studies ' for details.*

All trials reported using random methods to generate the allocation sequence, but only Marquino 2003 mentioned the method, a table of random numbers. None of the trials referred to allocation concealment. None of the trials mentioned blinding, but they were unlikely to have used blinding based on the nature of the treatment regimens. Losses to follow up were high and no trial included all the enrolled participants in the final analysis. Karbwang 1994 and Thimasarn 1997 included more than 90% of the participants in the final analysis (adequate). It was not possible to calculate the losses to follow up for Smithius 2004, and all the other trials included less than 90% of the enrolled participants in the final analysis (inadequate).

Effects of interventions

We have stratified the trials based on the total dose of mefloquine, either 25 mg/kg or 15 mg/kg. Within these stratifications we have grouped the trials according to the total dose of artesunate. The total doses in milligrams per kilogram are in Table 3; for some trials, we converted the doses into milligrams per kilogram from a total dose in milligrams.

1. Mefloquine total dose: 25 mg/kg

a. Artesunate total dose: ≥ 10 mg/kg

Four trials: Looareesuwan 1992b, Nosten 1994b, Price 1995, and Thimasarn 1997

Treatment failure

There were statistically significantly fewer treatment failures for participants taking artesunate plus mefloquine at all time points: day 28 (RR 0.17, 95% CI 0.06 to 0.47; 824 participants, 4 trials), day 42 (RR 0.23, 95% CI 0.14 to 0.39; 298 participants, 1 trial), and day 63 (RR 0.26, 95% CI 0.09 to 0.77; 501 participants, 2 trials) (Analysis 1.1)

Parasitaemia

Artesunate plus mefloquine was associated with a statistically significant lower risk of parasitaemia at day three (RR 0.04, 95% CI 0.02 to 0.11; 716 participants, 2 trials), day seven (RR 0.02, 95% CI 0.00 to 0.11; 700 participants, 2 trials), and day 14 (RR 0.09, 95% CI 0.03 to 0.28; 339 participants, 1 trial) (Analysis 2.2)

Resolution of fever

Nosten 1994b reported fewer participants still with fever in the artesunate plus mefloquine group at day two (RR 0.22, 95% CI 0.11 to 0.45; 348 participants) and day three (RR 0.02, 95% CI 0.00 to 0.38; 348 participants). Looareesuwan 1992b reported shorter fever clearance times with artesunate plus mefloquine (MD -32.20, 95% CI -46.54 to -17.86; 76 participants) (Analysis 1.1 and Analysis 1.4)

Parasite clearance

Looareesuwan 1992b reported shorter parasite clearance times with artesunate plus mefloquine (MD -26.00, 95% CI -34.81 to -17.19; 76 participants) (Analysis 1.5)

Adverse events

The results for Nosten 1994a and Nosten 1994b, for psychosis and vomiting, are combined under Nosten 1994a because the

single publication containing these two trials did not provide a breakdown by trial.

Generally, the adverse events were similar for the two treatment groups although headache and nausea were statistically significantly more frequent in the mefloquine only group. One participant in the mefloquine group had a serious adverse event (frank psychosis requiring hospitalization; 1/183 versus 0/185) and another had treatment discontinued due to severe vomiting (1/183 versus 0/185) (Analysis 1.6)

b. Artesunate total dose: 4 mg/kg

Two trials: Nosten 1994a and Karbwang 1994

Treatment failure

Artesunate plus mefloquine tended to perform better than mefloquine alone, but the effect was not statistically significant (RR 0.83, 95% CI 0.50 to 1.38; 259 participants, 2 trials). Although the point estimates for the individual trials are in opposite directions, the confidence intervals overlap. Karbwang 1994 also reported on treatment failure at day 42: four of 12 participants in the artesunate plus mefloquine group failed treatment compared with one of eight in the mefloquine group. This very small trial has low statistical power to detect differences, and thus results should be interpreted with caution (Analysis 2.1)

Parasitaemia

Artesunate plus mefloquine tended to reduce the risk of parasitaemia at days three and seven in Nosten 1994a, but the effect was only statistically significant at day three (RR 0.26, 95% CI 0.11 to 0.62; 280 participants). Karbwang 1994 reported on parasitaemia at day 14, but the results are difficult to interpret because of the very small numbers (Analysis 2.2) .

Resolution of fever

Fever resolved statistically significantly faster in participants in the artesunate plus mefloquine group at day two (RR 0.37, 95% CI 0.19 to 0.74; 239 participants) and day three (RR 0.33, 95% CI 0.12 to 0.89; 239 participants) in Nosten 1994a. These results were statistically significant unlike the shorter mean fever clearance times reported for the artesunate plus mefloquine group in Karbwang 1994 (Analysis 2.3 and Analysis 2.4)

Parasite clearance

Karbwang 1994 reported shorter mean parasite clearance times for the artesunate plus mefloquine group, but the difference was not statistically significant (Analysis 2.5)

Adverse events

Karbwang 1994 did not give details of adverse events but reported that nausea, vomiting, diarrhoea, dizziness, and bradycardia were similar for the two treatment groups. The single publication reporting on Nosten 1994a and Nosten 1994b did not give a breakdown of adverse events by trial; they are reported under Nosten 1994a in the meta-analysis.

2. Mefloquine total dose: 15 mg/kg

a. Artesunate total dose: 12 mg/kg

One trial: Marquino 2003

Parasitaemia

Fewer participants had parasitaemia in the artesunate plus mefloquine group on day three (RR 0.80, 95% CI 0.01 to 0.57; 98 participants) (Analysis 3.1)

Resolution of fever

There was no difference in resolution of fever between the two treatment groups, but the participant numbers were very small and confidence intervals wide (Analysis 3.2).

Adverse events

Insomnia was reported in one participant in the mefloquine group (Analysis 3.3).

b. Artesunate total dose: 4 mg/kg

One trial: Smithius 2004

Treatment failure

Levels of treatment failure were similar across the two treatment groups at days 14, 28, and 42 (Analysis 4.1).

Parasitaemia

There were similar results for parasitaemia at day three although more participants in the mefloquine group had positive blood slides (10/80 versus 4/76 for mefloquine and artesunate plus mefloquine, respectively) (Analysis 4.2).

Resolution of fever

Nine of 76 participants on artesunate plus mefloquine compared with seven of 78 participants on mefloquine still had documented fever at day three (Analysis 4.3)

Adverse events

This trial did not comment on adverse events.

DISCUSSION

This review includes 1155 participants from eight trials. The data are mainly from South-East Asia where malaria transmission is low and multiple-drug resistance is prevalent.

Few trials reported the number of participants screened and eligible, the numbers excluded or withdrawn, or the numbers lost to follow up in each treatment group at each target visit. Where possible we used the randomized participants to form our denominator (approximated intention-to-treat analyses), but where this information was unavailable we used the numbers as given in the trial report. It was not clear from the trial reports if any of the trials that concealed allocation of treatment also used blinding, but based on the description of the regimens this was unlikely. This might affect the quality of trial results by introducing bias and therefore limiting the conclusions that can be made.

Although some trials included both children and adults, we were unable to analyse outcomes by age group because the trial reports did not provide details.

Few participants contributed to each given outcome because of a lack of uniformity in the way the trials measured and reported on outcomes, and in the drug doses and regimens. This creates

uncertainty with the observed result and some comparisons did not have much statistical power to detect differences.

The combination of artesunate and mefloquine generally results in higher cure rate and better fever control than mefloquine alone. A total dose of 25 mg/kg mefloquine and at least 10 mg/kg artesunate gave the best results. The effects were more varied with a lower dose of artesunate (4 mg/kg), but the combination was still better than mefloquine alone. There were insufficient data to determine the effect of using at least 10 mg/kg artesunate and 15 mg/kg mefloquine. The combination of 4 mg/kg artesunate and 15 mg/kg mefloquine did not perform better than mefloquine alone.

One serious adverse event (psychosis) was observed in the mefloquine alone group. Other adverse events were similar across treatment groups, sometimes leading to discontinuation of treatment. Because the number of participants is still small to enable the risk of rare but important adverse events to be determined, surveillance of artesunate plus mefloquine is needed.

AUTHORS' CONCLUSIONS

Implications for practice

Artesunate plus mefloquine is better than mefloquine alone for clearing malaria parasites and resolving fever in people with uncomplicated *P. falciparum* malaria in areas with low malaria transmission, although the trials reviewed were of variable methodological quality. Adding artesunate to mefloquine does not lead to any more adverse events than when mefloquine is used alone. A total dose of 25 mg/kg mefloquine and at least 10 mg artesunate lead to faster symptom relief and better cure. There are insufficient data to determine the effect of using lower doses of mefloquine.

Implications for research

Randomized controlled trials are needed from areas outside of South-East Asia, as are trials in children. These trials need to determine the optimal regimen of artesunate plus mefloquine and should use uniform outcome definitions and standardized reporting to allow for comparability of results. Trials should also include outcomes on symptom resolution as these are of particular interest to malaria patients. Trialists should use rigorous methodology, particularly for allocation concealment and blinding, and thorough reporting.

2008: As monotherapy is no longer recommended by the World Health Organization for malaria treatment (WHO 2006), the authors do not intend to update this review.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Karbwang 1994

Methods	Randomized controlled trial Length of follow up: 42 d Generation of allocation sequence: no details available Allocation concealment: not mentioned Blinding: not mentioned Inclusion of all randomized participants: 9.1% (2/22) excluded after randomization due to vomiting of trial drugs
Participants	Number enrolled: 22 participants aged 17 to 48 years Inclusion criteria: adult male patients; aged 17 to 48 years; 45 to 70 kg bodyweight; uncomplicated malaria; asexual parasites < 5% Exclusion criteria: history of liver or kidney disease
Interventions	1. Artesunate plus mefloquine 2. Mefloquine Artesunate: 200 mg Mefloquine: 750 mg followed by 500 mg 6 h later
Outcomes	1. Mean fever clearance time 2. Mean parasite clearance time 3. Adverse events 4. Parasite counts at various time points reportedly measured but not reported
Notes	Location: Bangkok, Thailand Date: not given Source of funding: UNDP/World Bank/WHO Special Programme for Training in Tropical Diseases, Atlantic Co. Ltd (Thailand), and Hoffmann-La Roche (Thailand)

Looareesuwan 1992a

Methods	Randomized controlled trial Length of follow up: 28 d Generation of allocation sequence: no details available Allocation concealment: not mentioned Blinding: not mentioned Inclusion of all randomized participants: 9.4% (8/85) excluded at day 28 from analysis due to severe vomiting of study drugs and concomitant illness but other losses to follow up were not accounted for
Participants	Number enrolled: 127 participants between 16 and 56 years old Inclusion criteria: acute uncomplicated falciparum malaria; 100 to 200,000 parasites/µL blood; 16 to 60 years old; 45 to 60 kg bodyweight who agreed to stay in hospital for 28 days Exclusion criteria: pregnancy; severe malaria; and history of antimalarial drug treatment in preceding 1 week
Interventions	1. Artesunate plus mefloquine 2. Mefloquine Artesunate: 100 mg followed by 50 mg/12 h for 5 d Mefloquine: 750 mg followed by 500 mg after 6 h Not included in this review: 3. Artesunate
Outcomes	1. Number cured at 28 d 2. Mean parasite clearance time 3. Mean fever clearance time 4. Adverse events
Notes	Location: Bangkok, Thailand Date: January to May 1991 Source of funding: Mahidol University research grant and Roche Research Foundation of Hong Kong; Atlantic Pharmaceutical Co. Ltd supplied artesunate tablets

Marquino 2003

Methods	Randomized controlled trial Length of follow up: 28 d Generation of allocation sequence: table of random numbers Allocation concealment: not mentioned Blinding: not mentioned Inclusion of all randomized participants: 14.8% (17/115) were excluded from analysis at day 28 because of loss to follow up and taking antimalarial medication outside of the trial

Marquino 2003 *(Continued)*

Participants	Number enrolled: 115 children and adults aged 5 to 50 years Inclusion criteria: falciparum mono infection with 500 to 30,000 parasites/µl of blood; axillary temperature at least 37.5 °C and/or history of fever in previous 48 h Exclusion criteria: severe malaria; presence of other causes of fever; pregnancy; and history of allergy to trial medication
Interventions	1. Artesunate plus mefloquine 2. Mefloquine Artesunate: 4 mg/kg/d for 3 d, single dose Mefloquine: 15 mg/kg, single dose
Outcomes	1. Fever on day 3 2. Parasite carriage at days 3, 7, 14, 21, and 28 3. Adverse events
Notes	Location: Peruvian Amazon Date: June to September 2000 Source of funding: US Agency for International Development, the US Naval Medical Research Command, and the Government of Peru

Nosten 1994a

Methods	Randomized controlled trial Length of follow up: 28 d Generation of allocation sequence: randomization in pairs, no further details available Allocation concealment: not mentioned Blinding: not mentioned Inclusion of all randomized participants: 21.4% (65/304) excluded at day 28 due to vomiting trial medication and loss to follow up
Participants	Number enrolled: 304 adults and children Inclusion criteria: slide-confirmed malaria; weight > 5 kg; no use of other antimalarial in previous month; no signs of severe disease; and not pregnant
Interventions	1. Artesunate plus mefloquine 2. Mefloquine Artesunate: 4 mg/kg, single dose Mefloquine: 25 mg/kg, single dose
Outcomes	1. Fever clearance time 2. Parasite clearance time 3. Parasite carriage at days 1, 2, 3, 4, 5, 7, 14, and 28 4. Adverse events
Notes	Location: Thai-Burmese boarder near Mae Sot Date: January to July 1992

Nosten 1994a *(Continued)*

	Source of funding: not reported
	Nosten 1994a and Nosten 1994b are published in the same article

Nosten 1994b

Methods	Randomized controlled trial
	Length of follow up: 63 d
	Generation of allocation sequence: no details
	Allocation concealment: not mentioned
	Blinding: not mentioned
	Inclusion of all randomized participants: 11.8% excluded at day 28 and 31.9% excluded at day 63 due to vomiting trial medication and attrition
Participants	Number enrolled: 348 adults and children
	Inclusion criteria: slide-confirmed malaria; weight > 5 kg; no use of other antimalarial in previous month; no signs of severe disease; and not pregnant
Interventions	1. Artesunate plus mefloquine 2. Mefloquine
	Artesunate: 4 mg/kg followed by 2 mg daily for 3 d
	Mefloquine: 25 mg/kg, single dose
Outcomes	1. Fever clearance time 2. Parasite clearance time 3. Parasite carriage at days 1, 2, 3, 4, 5, 7, 14, and 28 4. Adverse events
Notes	Location: Thai-Burmese boarder near Mae Sot
	Date: October 1992 to June 1993
	Source of funding: not reported
	Nosten 1994a and Nosten 1994b are published in the same article

Price 1995

Methods	Randomized controlled trial
	Length of follow up: 63 d
	Generation of allocation sequence: randomized in blocks of three, no further details available
	Allocation concealment: not mentioned
	Blinding: not mentioned

Price 1995 *(Continued)*

	Inclusion of all randomized participants: 14.1% (46/362) lost to follow up at day 28, and 28.3% (98/362) lost to follow up at day 63; participants excluded because of vomiting and for reasons reportedly unrelated to the trial
Participants	Number enrolled: 550 Inclusion criteria: weight at least 5 kg; slide-confirmed falciparum malaria; and no antimalarial treatment in preceding 63 d Exclusion criteria: pregnancy; signs of severe malaria or concomitant illness requiring hospitalization; and history of neuropsychiatric illness
Interventions	1. Artesunate plus mefloquine 2. Mefloquine Artesunate: 4 mg/kg/d for 3 d Mefloquine: 25 mg/kg, single dose on day 2 Not included in this review: 3. Artemether plus mefloquine
Outcomes	1. Parasite clearance time 2. Fever clearance time 3. Symptom clearance time 4. Adjusted cumulative failure rates at days 7, 28, 42, and 63 5. Adverse events
Notes	Location: Thai-Myanmar border Date: June 1993 to May 1994 Source of funding: Wellcome Trust of Great Britain

Smithius 2004

Methods	Randomized controlled trial Length of follow up: 42 d Generation of allocation sequence: not mentioned Allocation concealment: not mentioned Blinding: not mentioned Inclusion of all randomized participants: not possible to calculate losses to follow up because numbers were not clear
Participants	Number enrolled: 317, but only 156 given interventions relevant to this review Inclusion criteria: axillary temperature at least 37.5 °C or history of fever in previous 2 d; *Plasmodium falciparum* parasites of at least 1000/mm^3 blood Exclusion criteria: body weight < 5 kg; pregnant women; signs and symptoms of complicated malaria or suggestive of another cause of fever; patients with a recent history of mefloquine use; patients with a parasite count > 250,000/mm^3 and mixed infections
Interventions	1. Artesunate plus mefloquine 2. Mefloquine

Smithius 2004 *(Continued)*

	Artesunate: 4 mg/kg, single dose Mefloquine: 15 mg/kg, single dose Not included in this review: 3. Chloroquine 4. Sulfadoxine-pyrimethamine
Outcomes	1. Treatment failure at days 14, 28, and 42 2. Parasitaemia at day 3 3. Fever at day 3
Notes	Location: Kachin State, north Myanmar Date: July to August 2004 Source of funding: Médecins Sans Frontières (Holland)

Thimasarn 1997

Methods	Randomized controlled trial Length of follow up: 28 d Generation of allocation sequence: no details available Allocation concealment: not mentioned Blinding: not mentioned Inclusion of all randomized participants: 3% (12/394) excluded post-randomization for taking wrong regimen and vomiting of trial drugs but distribution across groups not given
Participants	Number enrolled: 394 participants Inclusion criteria: symptomatic adults > 15 years old with malaria contracted within 50 km radius of the trial clinics; asexual parasitaemia 500 to 400,000 parasites/µL blood; no signs of complications; no history of antimalarial drug intake in previous 2 weeks; and consent to stay in malaria free area for the period of follow up Exclusion criteria: pregnancy
Interventions	1. Artesunate plus mefloquine 2. Mefloquine Artesunate: 300 mg/d for 2 d Mefloquine: 750 mg on day 1 and 500 mg on day 2 Not included in this review: 3. Artesunate 4. Artemether 5. Quinine 6. Artemether-mefloquine 7. Artesunate plus mefloquine with a different mefloquine dose
Outcomes	1. Cure rate at day 28 2. Adverse events Not included in this review: 3. Parasite malaria drug sensitivity 4. Parasite malaria drug resistance

Thimasarn 1997 *(Continued)*

Notes	Location: Thai-Cambodia border Date: July 1993 to December 1994 Source of funding: World Health Organization country budget for Thailand (THA/DPC/001)

Allocation concealment: B = unclear, see 'Methods of the review' for details and a summary of the quality assessment in Table 04

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Adam 2005	Used different mefloquine doses for combination and mefloquine alone study arms
Cardoso 1996	Used different mefloquine doses for combination and mefloquine alone study arms
Looareesuwan 1993	Used different mefloquine doses for combination and mefloquine alone study arms
Luxemburger 1991	Used different mefloquine doses for combination and mefloquine alone study arms
Price 1998	Compared artesunate plus mefloquine with artesunate rather than mefloquine

DATA AND ANALYSES

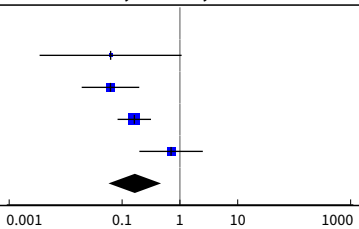
Comparison 1. Artesunate (AS) (≥ 10 mg) plus mefloquine (MQ) versus MQ (25 mg)

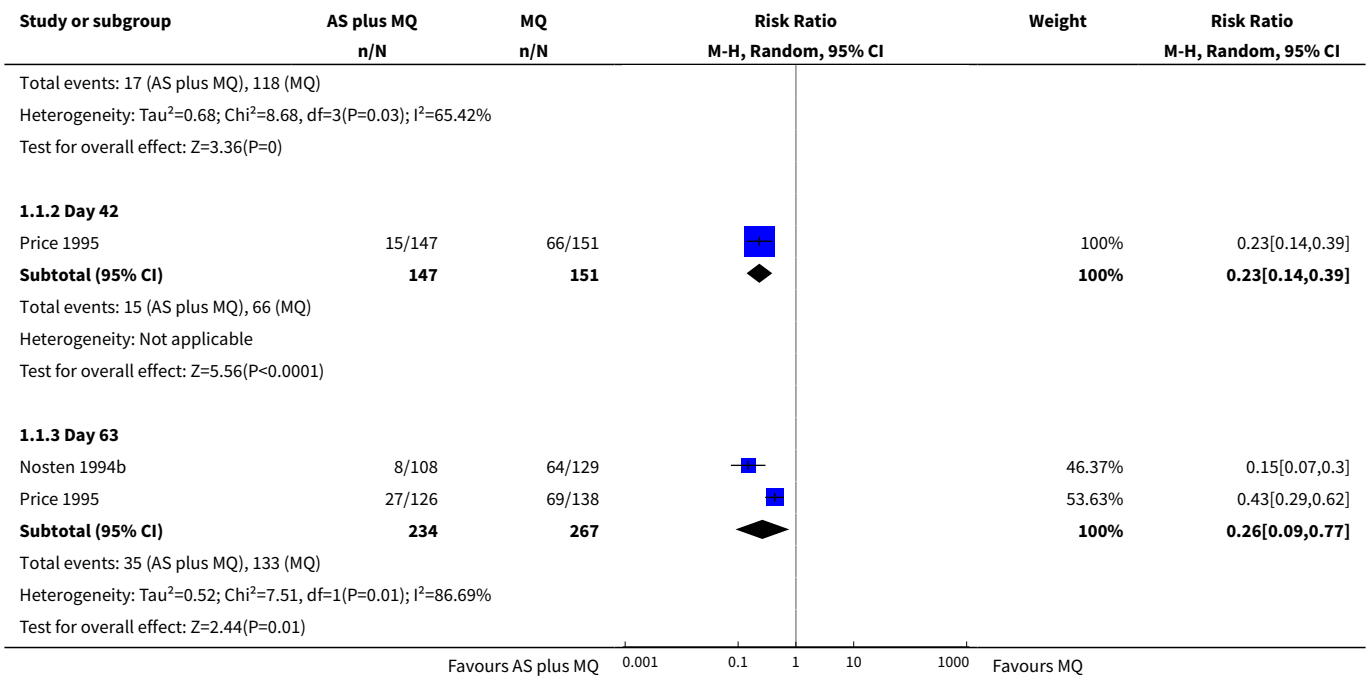
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Day 28	4	824	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.06, 0.47]
1.2 Day 42	1	298	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.14, 0.39]
1.3 Day 63	2	501	Risk Ratio (M-H, Random, 95% CI)	0.26 [0.09, 0.77]
2 Parasitaemia	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Day 3	2	716	Risk Ratio (M-H, Fixed, 95% CI)	0.04 [0.02, 0.11]
2.2 Day 7	2	700	Risk Ratio (M-H, Fixed, 95% CI)	0.02 [0.00, 0.11]
2.3 Day 14	1	339	Risk Ratio (M-H, Fixed, 95% CI)	0.09 [0.03, 0.28]
3 Fever	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 Day 2	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Day 3	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Mean fever clearance time (h)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5 Mean parasite clearance time (h)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6 Adverse events	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Serious adverse events	1	368	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 8.04]
6.2 Adverse events requiring discontinuation of treatment	2	444	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.04, 3.23]
6.3 Abdominal pain	2	196	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.31, 1.20]
6.4 Cardiovascular abnormalities	1	120	Risk Ratio (M-H, Random, 95% CI)	1.95 [0.08, 46.79]
6.5 Central nervous system abnormalities	1	120	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.53, 1.36]
6.6 Diarrhoea	2	196	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.48, 2.77]
6.7 Dizziness	1	76	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.10, 1.24]
6.8 Headache	2	196	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.38, 0.69]
6.9 Itching and rash	1	76	Risk Ratio (M-H, Random, 95% CI)	2.85 [0.12, 67.83]
6.10 Nausea	2	196	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.33, 1.16]
6.11 Palpitations/anxiety	1	368	Risk Ratio (M-H, Random, 95% CI)	2.97 [0.12, 72.38]
6.12 Psychosis	1	654	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.01, 7.91]
6.13 Vomiting	4	1218	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.39, 1.62]
6.14 Other adverse events	1	120	Risk Ratio (M-H, Random, 95% CI)	8.43 [0.49, 146.28]

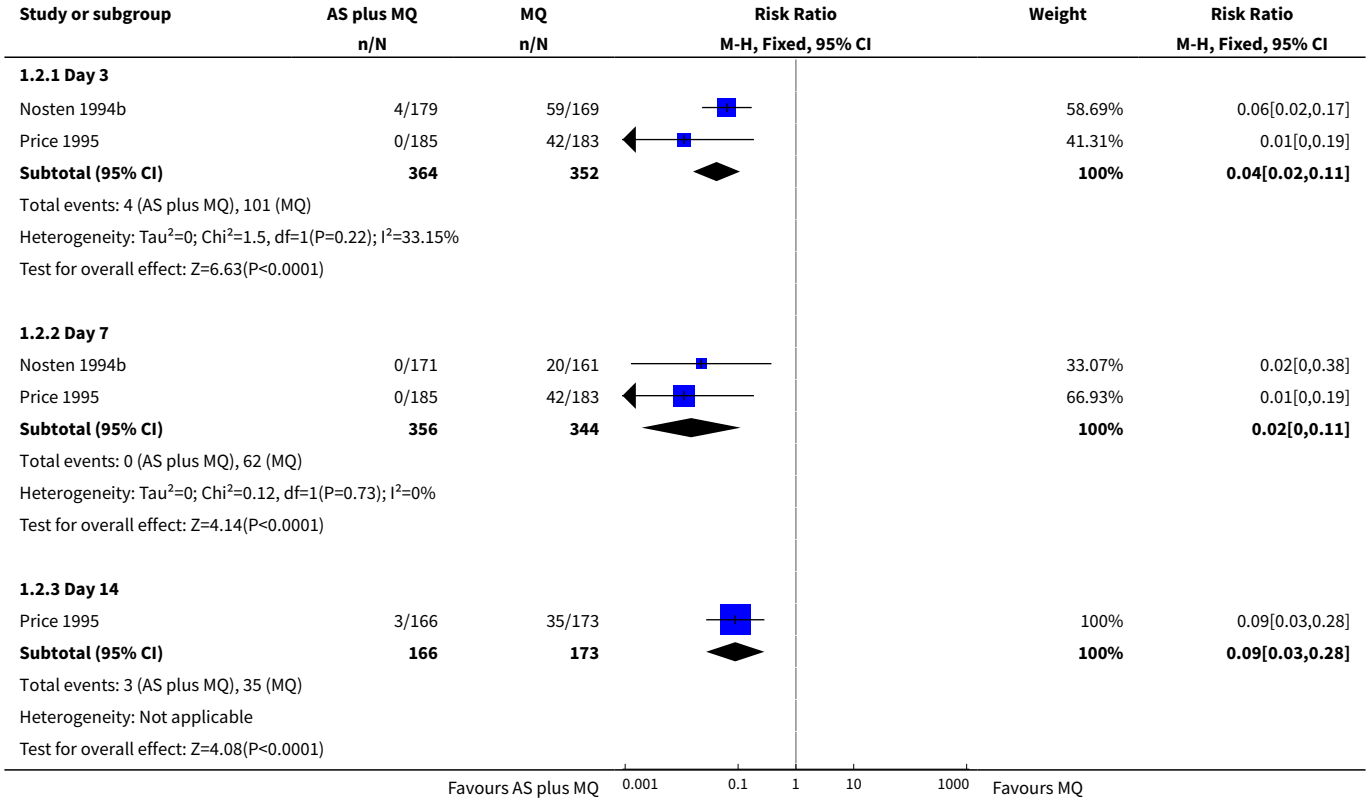
Analysis 1.1. Comparison 1 Artesunate (AS) (≥ 10 mg) plus mefloquine (MQ) versus MQ (25 mg), Outcome 1 Treatment failure.

Study or subgroup	AS plus MQ n/N	MQ n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Day 28					
Looareesuwan 1992a	0/39	7/37		10.34%	0.06[0,1.07]
Nosten 1994b	3/153	48/154		27.89%	0.06[0.02,0.2]
Price 1995	9/153	59/163		35.76%	0.16[0.08,0.32]
Thimasarn 1997	5/80	4/45		26.01%	0.7[0.2,2.49]
Subtotal (95% CI)	**425**	**399**		**100%**	**0.17[0.06,0.47]**



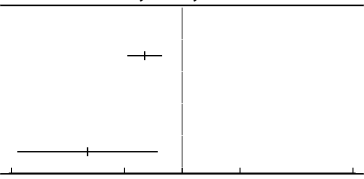


Analysis 1.2. Comparison 1 Artesunate (AS) (≥ 10 mg) plus mefloquine (MQ) versus MQ (25 mg), Outcome 2 Parasitaemia.



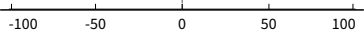
Analysis 1.3. Comparison 1 Artesunate (AS) (≥ 10 mg) plus mefloquine (MQ) versus MQ (25 mg), Outcome 3 Fever.

Study or subgroup	AS plus MQ n/N	MQ n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
1.3.1 Day 2				
Nosten 1994b	9/179	38/169		0.22[0.11,0.45]
1.3.2 Day 3				
Nosten 1994b	0/179	20/169		0.02[0,0.38]



Analysis 1.4. Comparison 1 Artesunate (AS) (≥ 10 mg) plus mefloquine (MQ) versus MQ (25 mg), Outcome 4 Mean fever clearance time (h).

Study or subgroup	AS plus MQ N	AS plus MQ Mean(SD)	MQ N	MQ Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Looareesuwan 1992a	39	37.5 (24.6)	37	69.7 (37.5)		-32.2[-46.54,-17.86]

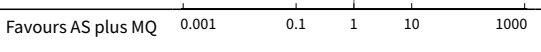


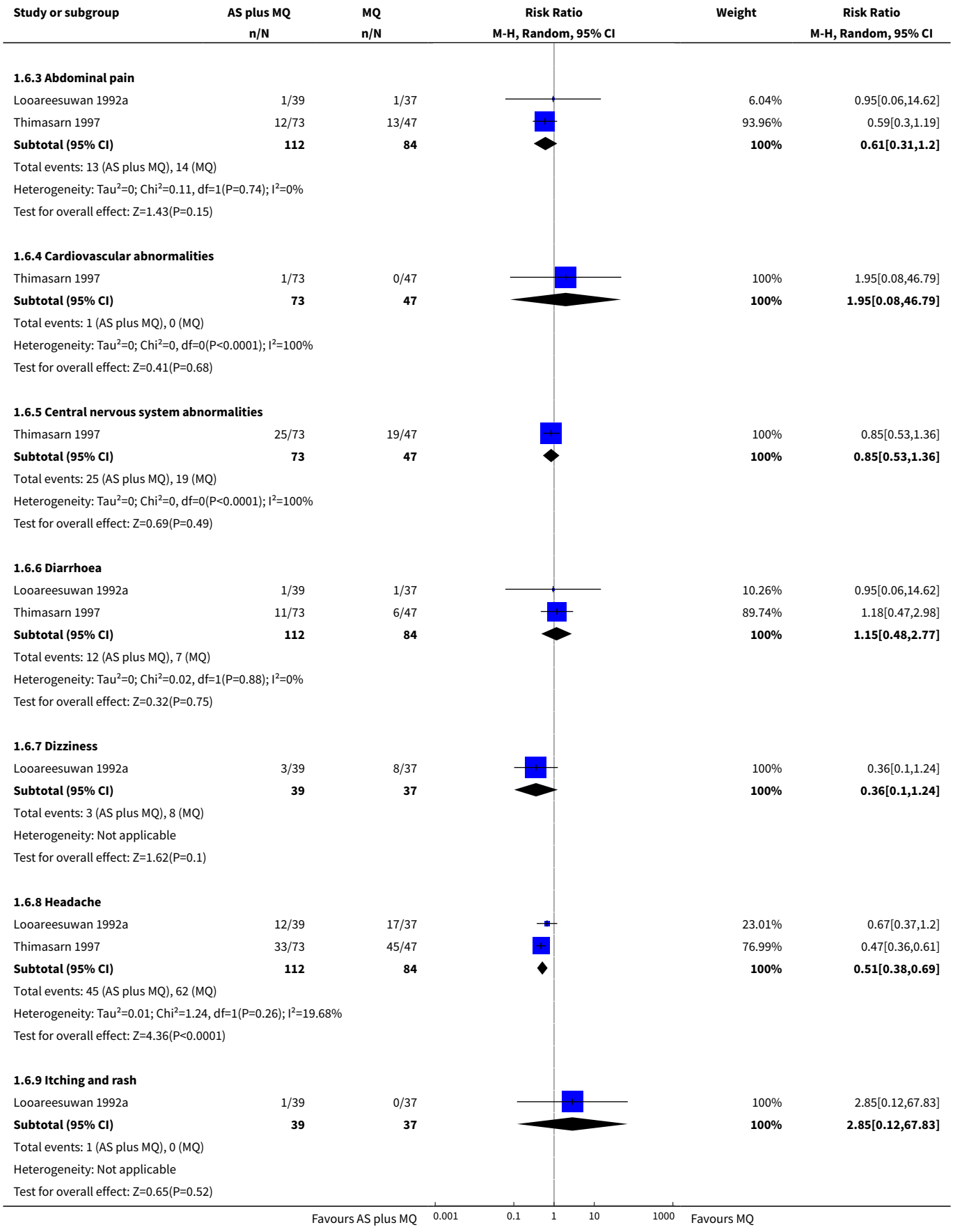
Analysis 1.5. Comparison 1 Artesunate (AS) (≥ 10 mg) plus mefloquine (MQ) versus MQ (25 mg), Outcome 5 Mean parasite clearance time (h).

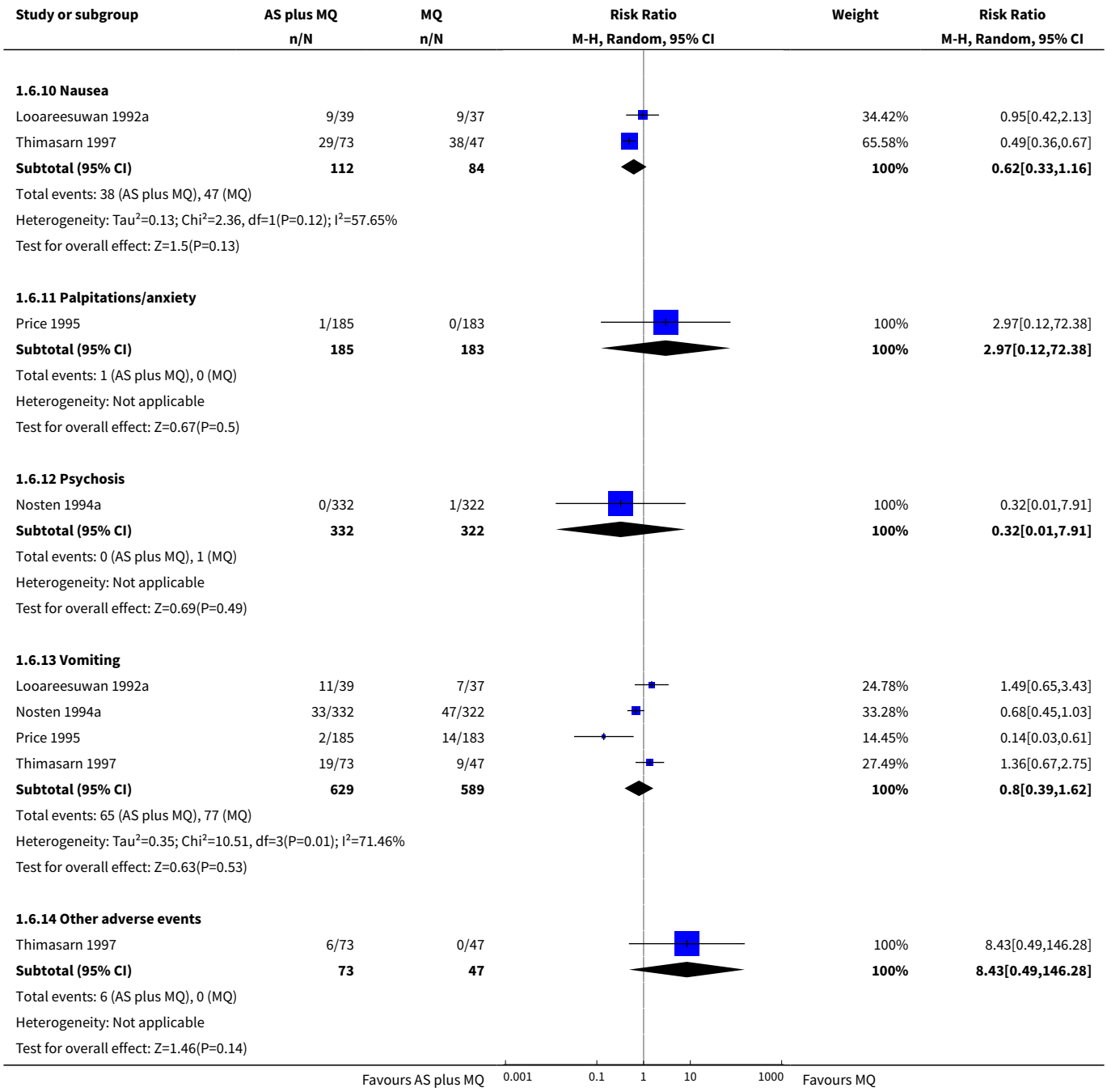
Study or subgroup	AS plus MQ N	AS plus MQ Mean(SD)	MQ N	MQ Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Looareesuwan 1992a	39	37.5 (10.1)	37	63.5 (25.5)		-26[-34.81,-17.19]

Analysis 1.6. Comparison 1 Artesunate (AS) (≥ 10 mg) plus mefloquine (MQ) versus MQ (25 mg), Outcome 6 Adverse events.

Study or subgroup	AS plus MQ n/N	MQ n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.6.1 Serious adverse events					
Price 1995	0/185	1/183		100%	0.33[0.01,8.04]
Subtotal (95% CI)	**185**	**183**		**100%**	**0.33[0.01,8.04]**
Total events: 0 (AS plus MQ), 1 (MQ)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.68(P=0.5)					
1.6.2 Adverse events requiring discontinuation of treatment					
Looareesuwan 1992a	0/37	1/39		50.38%	0.35[0.01,8.35]
Price 1995	0/185	1/183		49.62%	0.33[0.01,8.04]
Subtotal (95% CI)	**222**	**222**		**100%**	**0.34[0.04,3.23]**
Total events: 0 (AS plus MQ), 2 (MQ)					
Heterogeneity: $Tau^2=0$; $Chi^2=0$, df=1(P=0.98); $I^2=0\%$					
Test for overall effect: Z=0.94(P=0.35)					







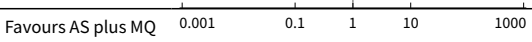
Comparison 2. Artesunate (AS) (4 mg) plus mefloquine (MQ) versus MQ (25 mg)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Day 28	2	259	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.50, 1.38]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.2 Day 42	1	20	Risk Ratio (M-H, Fixed, 95% CI)	2.67 [0.36, 19.71]
2 Parasitaemia	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Day 3	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Day 7	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Day 14	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Fever	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 Day 2	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Day 3	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Mean fever clearance time (h)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5 Mean parasite clearance time (h)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

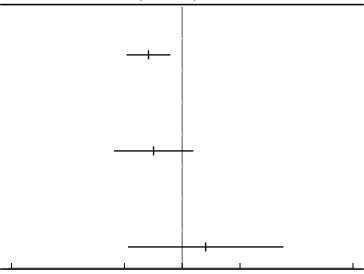
Analysis 2.1. Comparison 2 Artesunate (AS) (4 mg) plus mefloquine (MQ) versus MQ (25 mg), Outcome 1 Treatment failure.

Study or subgroup	AS plus MQ n/N	MQ n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 Day 28					
Karbwang 1994	3/12	1/8		4.42%	2[0.25,15.99]
Nosten 1994a	21/124	25/115		95.58%	0.78[0.46,1.31]
Subtotal (95% CI)	**136**	**123**		**100%**	**0.83[0.5,1.38]**
Total events: 24 (AS plus MQ), 26 (MQ)					
Heterogeneity: Tau^2=0; Chi^2=0.75, df=1(P=0.39); I^2=0%					
Test for overall effect: Z=0.71(P=0.48)					
2.1.2 Day 42					
Karbwang 1994	4/12	1/8		100%	2.67[0.36,19.71]
Subtotal (95% CI)	**12**	**8**		**100%**	**2.67[0.36,19.71]**
Total events: 4 (AS plus MQ), 1 (MQ)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.96(P=0.34)					



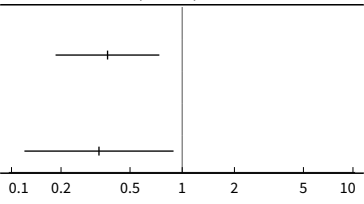
Analysis 2.2. Comparison 2 Artesunate (AS) (4 mg) plus mefloquine (MQ) versus MQ (25 mg), Outcome 2 Parasitaemia.

Study or subgroup	AS plus MQ n/N	MQ n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
2.2.1 Day 3				
Nosten 1994a	6/143	22/137		0.26[0.11,0.62]
2.2.2 Day 7				
Nosten 1994a	2/143	6/137		0.32[0.07,1.56]
2.2.3 Day 14				
Karbwang 1994	1/12	0/10		2.54[0.11,56.25]



Analysis 2.3. Comparison 2 Artesunate (AS) (4 mg) plus mefloquine (MQ) versus MQ (25 mg), Outcome 3 Fever.

Study or subgroup	AS plus MQ n/N	MQ n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
2.3.1 Day 2				
Nosten 1994a	10/124	25/115		0.37[0.19,0.74]
2.3.2 Day 3				
Nosten 1994a	5/124	14/115		0.33[0.12,0.89]

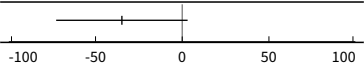


Analysis 2.4. Comparison 2 Artesunate (AS) (4 mg) plus mefloquine (MQ) versus MQ (25 mg), Outcome 4 Mean fever clearance time (h).

Study or subgroup	AS plus MQ N	AS plus MQ Mean(SD)	MQ N	MQ Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Karbwang 1994	12	31.2 (12.4)	8	44.7 (43.1)		-13.5[-44.18,17.18]

Analysis 2.5. Comparison 2 Artesunate (AS) (4 mg) plus mefloquine (MQ) versus MQ (25 mg), Outcome 5 Mean parasite clearance time (h).

Study or subgroup	AS plus MQ N	AS plus MQ Mean(SD)	MQ N	MQ Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Karbwang 1994	12	47.5 (19.6)	8	82.3 (52.3)		-34.8[-72.7,3.1]

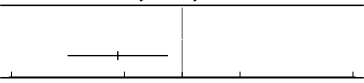


Comparison 3. Artesunate (AS) (≥ 10 mg) plus mefloquine (MQ) versus MQ (15 mg)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Parasitaemia	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Day 3	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Fever	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Day 3	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Adverse event	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Insomnia	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

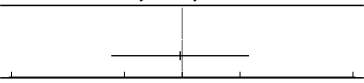
Analysis 3.1. Comparison 3 Artesunate (AS) (≥ 10 mg) plus mefloquine (MQ) versus MQ (15 mg), Outcome 1 Parasitaemia.

Study or subgroup	AS plus MQ n/N	MQ n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
3.1.1 Day 3				
Marquino 2003	1/51	12/47		0.08[0.01,0.57]



Analysis 3.2. Comparison 3 Artesunate (AS) (≥ 10 mg) plus mefloquine (MQ) versus MQ (15 mg), Outcome 2 Fever.

Study or subgroup	AS plus MQ n/N	MQ n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
3.2.1 Day 3				
Marquino 2003	1/51	1/47		0.92[0.06,14.32]



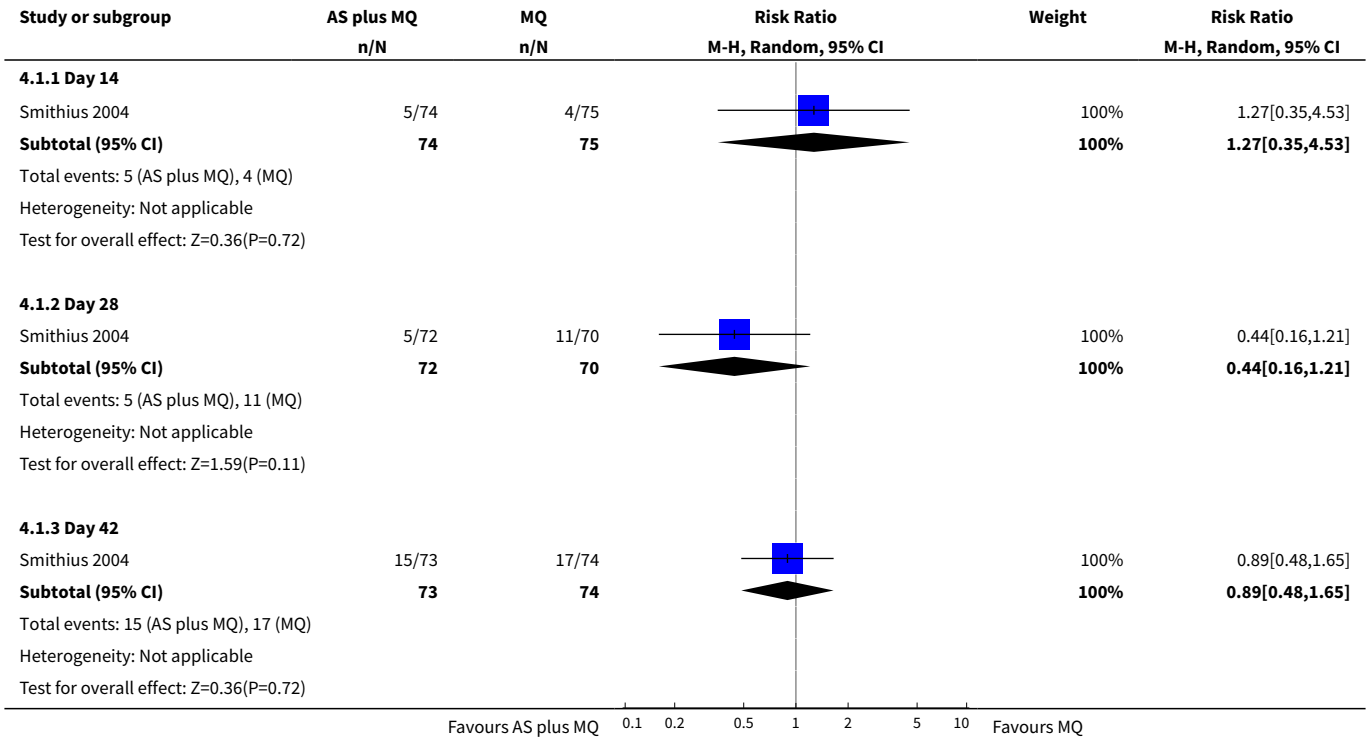
Analysis 3.3. Comparison 3 Artesunate (AS) (≥ 10 mg) plus mefloquine (MQ) versus MQ (15 mg), Outcome 3 Adverse event.

Study or subgroup	AS plus MQ n/N	MQ n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
3.3.1 Insomnia				
Marquino 2003	0/51	1/47		0.31[0.01,7.37]

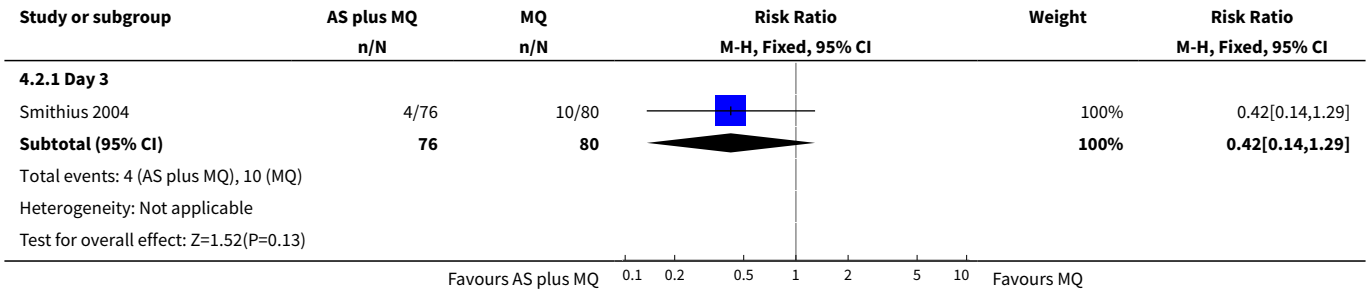
Comparison 4. Artesunate (AS) (4 mg) plus mefloquine (MQ) versus MQ (15 mg)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Day 14	1	149	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.35, 4.53]
1.2 Day 28	1	142	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.16, 1.21]
1.3 Day 42	1	147	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.48, 1.65]
2 Parasitaemia	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Day 3	1	156	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.14, 1.29]
3 Fever	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 Day 3	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

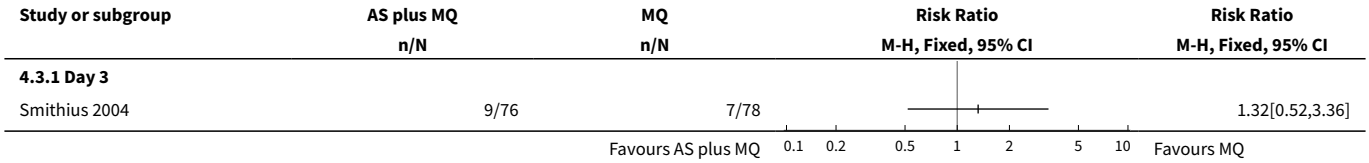
Analysis 4.1. Comparison 4 Artesunate (AS) (4 mg) plus mefloquine (MQ) versus MQ (15 mg), Outcome 1 Treatment failure.



Analysis 4.2. Comparison 4 Artesunate (AS) (4 mg) plus mefloquine (MQ) versus MQ (15 mg), Outcome 2 Parasitaemia.



Analysis 4.3. Comparison 4 Artesunate (AS) (4 mg) plus mefloquine (MQ) versus MQ (15 mg), Outcome 3 Fever.



ADDITIONAL TABLES

Table 1. Detailed search strategies

Search set	CIDG SR[a]	CENTRAL	MEDLINE[b]	EMBASE[b]	LILACS[b]	BIOSIS
1	artesunate	artesunate	ARTESUNATE	ARTESUNATE	artesunate	artesunate
2	mefloquine	mefloquine	artesunate	artesunate	mefloquine	mefloquine
3	Lariam	Lariam	arsumax	arsumax	malaria	Lariam
4	—	2 or 3	1 or 2 or 3	1 or 2 or 3	1 and 2 and 3	—
5	—	1 and 4	MEFLOQUINE	mefloquine	—	—
6	—	—	mefloquine	MEFLOQUINE	—	—
7	—	—	Lariam	mephaquim	—	—
8	—	—	5 or 6 or 7	Lariam	—	—
9	—	—	4 and 8	5 or 6 or 7 or 8	—	—
10	—	—	exp MALARIA	4 and 9	—	—

Table 1. Detailed search strategies *(Continued)*

11	—	—	malaria	malaria	—	—
12	—	—	exp PLASMODIUM	MALARIA	—	—
13	—	—	plasmodium	PLASMODIUM-FALCIPARUM	—	—
14	—	—	10 or 11 or 12 or 13	11 or 12 or 13	—	—
15	—	—	9 and 14	10 and 14	—	—

[a]Cochrane Infectious Diseases Group Specialized Register.
[b]Search terms used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration Higgins 2005; upper case: MeSH or EMTREE heading; lower case: free text term.

Table 2. Methods for future updates

Method	Details
Recrudesced and new infections	In areas of intense malaria transmission, blood smears positive for malaria parasites after day 14 may be a result of new infections or a recrudescence of the original infection. Polymerase chain reaction (PCR) is a method that can be used to differentiate between new and old infections. We will use the results of PCR analyses, if they become available, to differentiate between recrudesced and new infections
Continuous data reported with geometric means	We will extract the standard deviations on the log scale, and extract minimum and maximum values for medians. We will combine the findings on a log scale and report on the original scale; we will report medians and ranges in tables
Exploring potential sources of heterogeneity using subgroup analyses	1. Intervention: simultaneous versus sequential regimens; mefloquine dose; and artesunate dose 2. Trial setting: level of background mefloquine resistance; high malaria transmission (an area of hyperendemicity or holoendemicity) versus low transmission (an area of hypoendemicity or mesoendemicity) 3. Pre-treatment malaria parasite density: < 250,000/µL or 5% of total red blood cells and at least 250,000/µL or 5% of total red blood cells 4. Age: ≤ 5 years and > 5 years
Sensitivity analyses	We will conduct sensitivity analyses for each of the components of methodological quality
Funnel plots	We will examine funnel plots for asymmetry, keeping in mind that the asymmetry could be caused by publication bias, differences in methodological quality, or heterogeneity

Table 3. Total dose and regimens: artesunate and mefloquine

Trial	Artesunate		Mefloquine	
	Total dose (mg/kg)	Regimen	Total dose (mg/kg)	Regimen
Karbwang 1994	3.33[a]	1 dose	21[b]	2 doses over 1 day
Looareesuwan 1992a	10	11 doses over 5 days	21[b]	2 doses over 1 day

Table 3. Total dose and regimens: artesunate and mefloquine *(Continued)*

Marquino 2003	12	3 doses over 3 days	15	1 dose
Nosten 1994a	4	1 dose	25	1 dose
Nosten 1994b	10	4 doses over 3 days	25	1 dose
Price 1995	12	3 doses over 3 days	25	1 dose
Smithius 2004	4	1 dose	15	1 dose
Thimasarn 1997	10[a]	2 doses over 2 days	21[b]	2 doses over 3 days

[a]Assuming 60 kg person (actual dose 200 mg).
[b]Assuming 60 kg person (actual dose 1250 mg).

Table 4. Risk of bias assessment

Trial	Generation of allocation sequence[c]	Allocation concealment[d]	Blinding[e]	Inclusion of all randomized participants in final analysis[b]
Karbwang 1994	Unclear	Unclear	Unclear	Adequate
Looareesuwan 1992a	Unclear	Unclear	Unclear	Inadequate
Marquino 2003	Adequate	Unclear	Unclear	Inadequate
Nosten 1994a	Unclear	Unclear	Unclear	Inadequate
Nosten 1994b	Unclear	Unclear	Unclear	Inadequate
Smithius 2004	Unclear	Unclear	Unclear	Inadequate
Thimasarn 1997	Unclear	Unclear	Unclear	Adequate
Price 1998	Unclear	Unclear	Unclear	Inadequate

[a]See the 'Assessment of risk of bias in included studies' for the assessment methods, and the Characteristics of included studies' for the methods used in each trial.
[b]For primary outcomes.
[c]Unclear: reported as random but method not revealed.
[d]Unclear: not mentioned.
[e]Unclear: unlikely to be blinded.

WHAT'S NEW

Date	Event	Description
14 March 2012	Amended	The CIDG is piloting a new classification system for reviews. The classification for this review has now been added; description included in "Published notes" section of review

Date	Event	Description
13 August 2008	Review declared as stable	As monotherapy is no longer recommended by the World Health Organization for malaria treatment (WHO 2006), the authors do not intend to update this review.

HISTORY

Protocol first published: Issue 4, 2003
Review first published: Issue 4, 2005

Date	Event	Description
13 August 2008	Amended	Converted to new review format and minor editing.

CONTRIBUTIONS OF AUTHORS

Hasifa Bukirwa extracted and analysed data, and drafted the review. Lois Orton extracted data, and edited and advised on the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Liverpool School of Tropical Medicine, UK.

External sources

- Department for International Development, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We changed the title of the review from 'Artesunate plus mefloquine for treating malaria' to the current title to reflect the review's inclusion criteria. We include only one primary outcome measure, treatment failure, following recent developments in knowledge around the accuracy of some malaria treatment outcomes. In line with changes in the guidance from the Cochrane Infectious Diseases Group, we updated the methods for assessing blinding and changed the wording of "loss to follow up" to "inclusion of all randomized participants in the final analysis".

NOTES

2012, Issue 4: Status: Historical question – no update intended: monotherapy no longer recommended

As of August 2008, this Cochrane Review is no longer being updated. The question addressed by this Cochrane Review is no longer considered to be relevant to decision making, as monotherapy has been replaced by Artemisinin-based combination therapy, and is no longer used. For the most up-to-date information regarding malaria treatments, please see: Sinclair D, Zani B, Donegan S, Olliaro P, Garner P. Artemisinin-based combination therapy for treating uncomplicated malaria. Cochrane Database of Systematic Reviews 2009, Issue 3. Art. No.: CD007483. DOI: 10.1002/14651858.CD007483.pub2

The review status is a pilot system used by the Cochrane Infectious Diseases Group to help the reader understand whether the review is concerns a current question, and is up to date.

We report on:

1. The question the review addresses. Is it a:

- **Historical question,** where the intervention or policy has been superseded by new medical developments (such as a new drug); or a

- **Current question**, which is still relevant to current policy or practice.

2. Whether the review is up to date. Is the review:

- **Up to date;**
- **Update pending**; or
- **No update intended**.

We then provide comment on the review status, to help explain the categories selected.

INDEX TERMS

Medical Subject Headings (MeSH)

Antimalarials [*therapeutic use]; Artemisinins [*therapeutic use]; Artesunate; Drug Therapy, Combination; Malaria, Falciparum [*drug therapy]; Mefloquine [*therapeutic use]; Sesquiterpenes [*therapeutic use]

MeSH check words

Humans